UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

VB

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/854,825	05/12/97	CHISARI F	329368-101CO

HM12/0202

ALLEN BLOOM ESQ.
DECHERT, PRICE AND RHOADS
P.O. BOX 5218
PRINCETON NJ 08543-5208

EXAMINER	
PARKIN, J	
ART UNIT	**PAPER NUMBER**
1641	16

DATE MAILED: 02/02/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/854,825	Chisari et al.
Examiner	**Group Art Unit**
Jeffrey S. Parkin, Ph.D.	1641

☒ Responsive to communication(s) filed on *8 Nov 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *22-25, 30, 32, 36, 40, and 44-66* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *22-25, 30, 32, 36, 40, and 44-66* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Detailed Office Action

Continued Prosecution Application

1.The request filed on 08 November, 1999, for a Continued Prosecution Application (CPA) under 37 C.F.R. § 1.53(d) based on parent Application No. 08/854,825 is acceptable and a CPA has been established.

Status of the Claims

2. Acknowledgement is hereby made of receipt of the Preliminary Amendment filed 08 November, 1999, wherein claims 22, 52, 56, 58, 60, and 62 were amended and new claims 65 and 66 submitted. Claims 22-25, 30, 32, 36, 40, and 44-66 are pending in the instant application. No new arguments accompanied the response.

35 U.S.C. § 112, First Paragraph

3. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 22-25, 30, 32, 36, 40, and 44-64, as well as, newly submitted claims 65 and 66, are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. *In re Rasmussen*, 650 F.2d 1212, 211 U.S.P.Q. 323 (C.C.P.A. 1981). *In re Wertheim*, 541 F.2d 257, 191 U.S.P.Q. 90

(C.C.P.A. 1976). Applicants have amended the claims to include the limitation "**no more than a total of two single amino acid substitutions, deletions, or insertions**" which does not receive adequate support in the disclosure. It is noted that the disclosure references (see p. 14, lines 14-25) functionally equivalent peptides that can be identified through "suitable single amino acid substitutions, deletions, or insertions". The disclosure also provides a listing of HCV peptides that may contain CTL epitopes (see p. 44-46), as well as, their further characterization to actually confirm the presence of such epitopes. However, the disclosure does not describe the preparation of HCV peptidic variants containing no more than a total of two single amino acid substitutions, deletions, or insertions. Accordingly, the skilled artisan would reasonably conclude that applicants were in possession of the specific peptides described in the disclosure. However, the skilled artisan would not conclude that applicants contemplated making and using peptidic variants with the presently claimed limitations.

5. Claims 22-25, 30, 32, 36, 40, 44-57, and 60-66 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Applicants have amended the claim language to include a limitation specifying that the peptides of interest contain "no more than a total of two single amino acid substitutions, deletions, or insertions" in the peptide of interest. The disclosure details the identification of seven HCV CTL epitopes corresponding to regions of the core (e.g., amino acids 131-140 and 178-187), NS3 (e.g., amino acids 1169-1177 and 1406-1415), NS4 (e.g., amino acids 1789-1797 and 1807-1816), and NS5 (e.g., amino acids 2252-2260) antigens

(refer to pages 52 and 55 of the specification). These peptides were used to identify HCV-specific CTL responses in HCV-infected patients and some were employed in the generation of murine HCV-specific CTL. Appropriately drafted claim language directed toward these embodiments would obviate the rejection.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). The disclosure fails to provide adequate guidance pertaining to a number of these considerations as follows: 1) The disclosure fails to provide sufficient guidance or direction pertaining to acceptable amino acid replacements, additions, or deletions within any given peptide that will result in retention of the desired immunological properties. The art teaches that single amino acid substitutions in any given CTL epitope can adversely effect binding to the appropriate MHC Class I molecule (Smith *et al.*, 1997; Bertoletti *et al.*, 1994; Johnson *et al.*, 1992; Couillin *et al.*, 1995; and, Hahn *et al.*, 1992). Moreover, the applicants themselves state (refer to page 5 of the disclosure) that "At the present time, it is difficult to predict from the sequence of an antigenic protein how the protein will be processed and which peptide portions will bind HLA class I molecules and be presented to CTL's. Binding motifs have been predicted for some HLA class I molecules based on sequence analysis of peptides eluted from these

molecules . . . However, not all peptides that match the motif will be recognized as CTL-recognizable epitopes. Moreover, even of the peptides that are processed and bind to HLA class I molecules, identifying which ones will contain CTL-recognizable epitopes is not yet predictable." Without any prior instruction, which amino acid substitutions could one practicing the invention introduce directly into the CTL epitope and still retain an MHC Class I-restricted CTL response?

2) The disclosure fails to provide sufficient guidance or direction concerning the effects of single amino acid substitutions, additions, or deletions on sequences flanking the disclosed CTL epitopes. The prior art teaches that flanking amino acid residues critically influence the degree of peptide processing and presentation (Del Val *et al.*, 1991; Hahn *et al.*, 1992; and, Eisenlohr *et al.*, 1992). As described in the preceding paragraph, it is difficult to predict what amino acid sequences are required for proper peptide processing by the host and how they influence CTL recognition and lysis. Eisenlohr *et al.* (1992) reported that CTL epitopic flanking amino acid residues were critical for the efficient processing and presentation of antigen to CTL. Flanking sequences were capable of either enhancing or abrogating peptide processing and recognition. Hahn *et al.* (1992) disclosed that a single amino acid substitution immediately flanking the recognized CTL epitope significantly curtailed CTL-mediated cell lysis. Additional CTL studies performed by Del Val *et al.* (1991) documented that "residues that directly flank the antigenic sequence in a protein critically influence the amount of naturally processed and presented antigenic peptide." Moreover, the art also teaches that mutations in CTL epitopes adversely affect extracellular antigen processing by altering the trimming of flanking residues in longer sequences and influencing the susceptibility of optimal epitopes to proteolytic degradation

(Smith *et al.*, 1997; Del Val *et al.*, 1991; Eisenlohr *et al.*, 1992). In the absence of further guidance, the skilled artisan cannot reasonably predict which amino acid substitutions, additions, and/or deletions should be incorporated into any given peptide.

3) The disclosure fails to teach which, of the myriad number of peptides encompassed by the claim language, can reasonably be expected to undergo efficient processing and presentation. The art teaches that the presence of an MHC class I binding motif in a peptide is not sufficient to confer binding to the appropriate class I molecule (Nayersina *et al.*, 1993; Bertoletti *et al.*, 1994; Couillin *et al.*, 1995; and, Eisenlohr *et al.*, 1992). However, the specification fails to provide appropriate guidance pertaining to this point and further suggests that the skilled artisan cannot reasonably make this determination (see preceding paragraph and page 5 of the disclosure).

4) The disclosure fails to provide adequate guidance pertaining to the immunological properties of any given putative CTL-epitope containing peptide. The art teaches that the capacity of a putative CTL epitope to bind to a class I molecule does not mean that the epitope will be immunogenic (Nayersina *et al.*, 1993; Couillin *et al.*, 1995; and, Eisenlohr *et al.*, 1992). The specification is silent concerning this caveat.

5) The disclosure fails to provide any guidance concerning the effects of MHC Class I polymorphisms upon CTL epitope recognition and processing. Hansen *et al.* (1993) disclose the presence of 41 different alleles for the HLA-A locus, 61 for the HLA-B locus, and 18 for the HLA-C locus. Studies by Koziel *et al.* (1993) demonstrated that different HLA-restricted cloned cell lines (obtained from HCV-infected patients) recognized divergent CTL epitopes. Furthermore, the applicants reported (pp. 51-52) that only 4 out of 8 patients with the same HLA haplotype (e.g., A2.1)

generated a CTL response to the aforementioned HCV oligopeptides. Monaco (1992) further discusses polymorphisms external to the MHC locus in the low molecular mass polypeptide (LMP) complex and transporter genes that may also result in the presentation of different epitopes of the same antigen to the T-cell repertoire. Without further instruction, which of the disclosed CTL epitopes could one practicing the invention use to elicit a CTL response in individuals with different or similar MHC Class I haplotypes? Which amino acid substitutions in the CTL epitope or flanking regions would result in retention of the CTL response in patients with different MHC Class I specificities. In addition to the aforementioned caveats pertaining to the selection of a suitable peptide, a number of additional factors would preclude the skilled artisan from practicing the invention as broadly as claimed. The art teaches that virally infected patients contain CTL epitopic variants with reduced HLA and T cell receptor binding capacities (Bertoletti *et al.*, 1994 and Couillin *et al.*, 1995). Furthermore, natural sequence variation in viruses, particularly in CTL epitopes, results in the generation of immune resistant viruses (Bertoletti *et al.*, 1994; Johnson *et al.*, 1992; and, Couillin *et al.*, 1995). Finally, the art also teaches that HCV-specific CTL may actually contribute to liver disease pathogenesis in chronically infected patients (Rehermann *et al.*, 1996). Thus, it is not readily manifest that even upon identification of the appropriate candidate peptide, that said peptide would generate HCV-specific CTL capable of providing an ameliorative response.

6) The breadth of the claim language encompasses an exceedingly large genus which is inadequately supported by the disclosure as set forth *supra*.

7) The disclosure fails to provide a sufficient number of working embodiments. While a small number of HCV CTL epitopes were identified, the disclosure does not describe any suitable peptidic

variants that retain the desired immunological properties.

Accordingly, when the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the invention as presently claimed. Applicants may obviate this rejection by directing the claim language toward those specific peptides that contain demonstrable HCV CTL epitopes and the requisite immunogenicity to stimulate high-titers of HCV-specific CTL.

6. Claims 58 and 59 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claims 58 and 59 are drawn toward pharmaceutical compositions comprising HCV-derived peptides. The term pharmaceutical has an art-recognized definition and pertains to the use of medicinal drugs to treat disease (refer to Dorland's medical dictionary, 1988, pp. 1271-1272; *In re Gardner*, 166 U.S.P.Q. 138-142 (1970 C.C.P.A.); *Ex parte Skuballa*, 12 U.S.P.Q.2d 1570 (1989 Bd. Pat. App. Int.)). As such, the claimed peptides would presumably be employed in the prevention or treatment of HCV infection, predominantly in humans since this represents the natural host.

The legal considerations that govern enablement determinations pertaining to undue experimentation are disclosed in *In re Wands*, 8 U.S.P.Q.2d 1400 (C.A.F.C. 1988) and *Ex parte Forman* 230 U.S.P.Q. 546 (PTO Bd. Pat. App. Int., 1986). The courts concluded that several factual inquiries should be considered when making such assessments including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the

predictability or unpredictability of the art and the breadth of the claims. *In re Rainer*, 52 C.C.P.A. 1593, 347 F.2d 574, 146 U.S.P.Q. 218 (1965). As set forth in the preceding rejection, a number of pragmatic scientific caveats would preclude the skilled artisan from practicing the claimed invention as follows:

1) The art teaches that mutations in CTL epitopes adversely affect binding to the appropriate MHC Class I molecule.

2) The art teaches that flanking amino acid residues critically influence the degree of peptide processing and presentation.

3) The art teaches that the presence of an MHC class I binding motif in a peptide is not sufficient to confer binding to the appropriate class I molecule.

4) The art teaches that the capacity of a putative CTL epitope to bind to a class I molecule does not mean that the epitope will be immunogenic.

5) The art teaches that virally infected patients contain CTL epitopic variants with reduced HLA and T cell receptor binding capacities.

6) The art teaches that natural sequence variation in viruses, particularly in CTL epitopes, results in the generation of immune resistant viruses.

7) The art teaches that HCV-specific CTL may actually contribute to liver disease pathogenesis in chronically infected patients.

Moreover, the use of the claimed peptides as therapeutics provides additional constraints that would preclude the skilled artisan from practicing the invention as set forth:

1) The disclosure fails to provide sufficient guidance demonstrating that a vigorous HCV-specific CTL response can be generated in humans, or other mammals, that will result in amelioration of the clinical sequelae associated with HCV infection. As previously set forth, Rehermann *et al.* (1996), observe that patients chronically infected with HCV develop HCV-

specific CTL, but these CTL response are unable to clear the infection or produce any immediate salubrious effects. The authors concluded (refer to Discussion, page 1439) that "these results and the published database suggest that **the CTL response probably contributes to disease pathogenesis but is not vigorous enough to eradicate the virus during chronic HCV infection in most patients.**"

2) The disclosure fails to identify the correlates of protective immunity as it pertains to HCV infection. Koziel *et al.* (1997), Koff (1993), and Prince (1994) review some of the hurdles associated with developing adoptive immunotherapy involving HCV-specific CTL to combat HCV infection. They note that the correlates of protective immunity remain to be elucidated. Patients, often vigorously, develop HCV-specific CTL responses, but these response are often inadequate and incapable of clearing the virus or providing any substantial ameliorative effects. A number of factors contribute toward this inadequate immune response including the presence of HCV variants that elude immune surveillance, the presence of variant HCV CTL epitopes with altered antigen processing, transport, and presentation properties, and allelic MHC variation within any given patient population. Moreover, Koff (1993) adds that "the general failure to identify a neutralizing, protective humoral immune response in HCV infection coupled with the data described by Farci et al. represent an awesome constellation of impediments to the development of a HCV vaccine."

3) The disclosure fails to provide appropriate *in vitro* systems for the propagation of HCV and assays for the study of infection of cytopathic effects. In order to identify putative therapeutic compounds, the skilled artisan must first have the requisite *in vitro* systems with which to propagate the infectious agent of interest and assays to determine the potential antiviral activity

of any given compound. The art teaches that these systems and assays are not available to the virologist pursuing HCV antivirals (Koff, 1993 and Prince, 1994). As Koff (1993) concludes, "The list of obstacles to the development of a hepatitis C vaccine is becoming formidable. Failure to propagate HCV in tissue culture, the absence of simple in vitro assays for infection or cytopathic effects . . . are well known but not insurmountable issues."

4) The disclosure fails to provide adequate testing of the proposed pharmaceuticals in an art-recognized animal model. Following the preliminary screening of putative antiviral candidates in *in vitro* assays, the skilled artisan generally employs a suitable animal model to further address concerns that are not evident or addressed by *in vitro* screening assays (i.e., pharmacological properties of the putative therapeutic). However, the art teaches that such models are not available to the skilled artisan trying to develop an anti-HCV compound (Koff, 1993). As Koff (1993) reports, "The list of obstacles to the development of a hepatitis C vaccine is becoming formidable . . . and the lack of a suitable small-animal model are well known but not insurmountable issues." Thus, when the aforementioned factors are considered *in toto*, it would clearly require undue experimentation to practice the invention as presently claimed.

35 U.S.C. § 112, Second Paragraph

7. The previous rejection of claims 22-25, 30, 32, 36, 40, and 44-64 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is hereby withdrawn in response to applicants' amendment.

Non-statutory Double Patenting

8. The non-statutory double patenting rejection, whether of the

obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 U.S.P.Q. 644 (C.C.P.A. 1969); *In re Vogel*, 422 F.2d 438, 164 U.S.P.Q. 619 (C.C.P.A. 1970); *In re Van Ornum*, 686 F.2d 937, 214 U.S.P.Q. 761 (C.C.P.A. 1982); *In re Longi*, 759 F.2d 887, 225 U.S.P.Q. 645 (Fed. Cir. 1985); and *In re Goodman*, 29 U.S.P.Q.2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. § 1.78(d). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. § 3.73(b).

9. Claims 22-25, 30, 32, 36, 40, and 44-66 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 11-33 of U.S. Patent No. 5,709,995. Applicants have indicated that a terminal disclaimer will be submitted upon the identification of allowable subject matter.

Correspondence

10. The Art Unit location of your application in the Patent and Trademark Office has changed. To facilitate the correlation of related papers and documents for this application, all future correspondence should be directed to **art unit 1641.**

11. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette,

1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

12. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1641

29 January, 2000